UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/590,479	07/20/2007	Luigi Giusto Spagnoli	026073-00007	9687

4372 7590 08/17/2010

ARENT FOX LLP
1050 CONNECTICUT AVENUE, N.W.
SUITE 400
WASHINGTON, DC 20036

EXAMINER
CANELLA, KAREN A

ART UNIT	PAPER NUMBER
1643	

NOTIFICATION DATE	DELIVERY MODE
08/17/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

DCIPDocket@arentfox.com
IPMatters@arentfox.com
Patent_Mail@arentfox.com

Office Action Summary	Application No.	Applicant(s)	
	10/590,479	SPAGNOLI ET AL.	
	Examiner	Art Unit	
	Karen A. Canella	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 May 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 5-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 5-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1, 11, 12 and 15 have been amended. Claims 1 and 5-21 are pending and under consideration.

Acknowledgement is made of the instant application as a National; Application under 35 U.S.C. 371. It is noted that the sequence listing of the PCT application discloses SEQ ID NO:1 as a 18-mer comprising the sequence "LANLTQ" versus the sequence listing of the instant application which discloses SEQ ID NO:1 as a 17-mer comprising the sequence "LANTQ". Applicant contends that the sequence listing of the PCT application was in error, but that the specification of the PCT application supports the instant SEQ ID NO: 1 on page 5, line 30. This has been considered and found persuasive with regard to the basis for the instant SEQ ID NO:1. However, it should be pointed out that the sequence of the instant SEQ ID NO:1 17-mer is not known to be a subsequence of any protein as evidenced by the search summary below:

```
     FILE 'REGISTRY' ENTERED AT 13:13:32 ON 12 AUG 2010
L1             0 SEA ABB=ON  QFNWVSRLANTQGEDQK/SQSP

     FILE 'DGENE' ENTERED AT 13:13:47 ON 12 AUG 2010
                RUN GETSEQ
                ---------
L2             0 SEA QFNWVSRLANTQGEDQK/SQSP

     FILE 'PCTGEN' ENTERED AT 13:14:20 ON 12 AUG 2010
                RUN GETSEQ
                ---------
L3             0 SEA QFNWVSRLANTQGEDQK/SQSP.
```

It is unclear if applicant is intending to claim an epitope found in a new clusterin protein, or if said epitope of SEQ ID NO:1 is totally synthetic but providing for an antibody which somehow specifically recognizes a non-glycosylated nuclear isoform of clusterin.

The instant application will therefore have priority to the Feb 17, 2005, but it is noted that for purpose of the prior art search, the filing date of the RM2004A000098 application will not be considered because applicant has not provided a translation of the foreign priority document.

It is also noted that RM2004A000098 application describes SEQ ID NO: as the 18-mer comprising the sequence "LANLTQ" (page 12) rather than the instant 17-mer SEQ ID NO:1 comprising the sequence "LANTQ".

The facts appear to suggest that the instant SEQ ID NO:1 is incorrect.

Applicant is required to provide clarification.

The rejection of claims 1 and 11 under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter is withdrawn in light of applicant's amendment.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The rejection of claim 11 under 35 U.S.C. 102(b) as being anticipated by Fogelman et al, (WO03/086326) is maintained for reasons of record. Claim 11 is drawn in part to an immunogenic antigenic epitope of at least one human clusterin isoform comprising SEQ ID NO:4. Folgelman et al disclose the peptide of Sequence Identifier 20 (page 4, lines 1-2), said peptide comprising the instant SEQ ID NO:4 at resides 4-18. The peptide of Folgelman et al meets the requirement of being antigenic, as said peptide can be bound by an antibody. The peptide also fulfills the specific requirement of "immunogenic" as any peptide can be immunogenic given the appropriate host and appropriate presentation of the peptide to said host.

```
PN   WO2006034056-A2.
PD   30-MAR-2006.
PF   16-SEP-2005; 2005WO-US033205.
PR   16-SEP-2004; 2004US-0610711P.
PA   (REGC ) UNIV CALIFORNIA.
PA   (UYAL-) UNIV ALABAMA RES FOUND.
PI   Fogelman AM,  Navab M,  Anantharamaiah G;
DR   WPI; 2006-263401/27.
PT   New peptide containing D-amino acid(s) and/or protecting group(s),
PT   ameliorates symptoms of inflammatory conditions, e.g. atherosclerosis or
PT   stroke, in mammals.
PS   Disclosure; SEQ ID NO 478; 135pp; English.
CC   This invention describes a novel G-type peptide capable of ameliorating
CC   symptoms of an inflammatory condition, comprising AEG87480 and AEG87986
CC   and incorporating D amino acid(s) and/or protecting group(s). The
CC   invention also describes; a) a stent for delivering drugs to a vessel in
CC   a body comprising a stent framework including reservoir, and active
CC   agent(s) and/or a small organic molecule positioned in the reservoirs; b)
CC   a method of manufacturing a drug-polymer stent comprising providing a
CC   stent framework; c) cutting reservoirs in the stent framework; d)
CC   applying a composition comprising the active agent(s) to the reservoir(s)
CC   and drying the composition; e) a method of treating a vascular condition
CC   by positioning a stent within a vessel of a body; f) expanding the stent
```

```
CC   and eluting active agent(s) from a surface of the stent and g) a method
CC   of synthesizing a peptide comprising providing different peptide fragment
CC   subsequences of the peptide and coupling the peptide fragment
CC   subsequences in solution phase to form the peptide. The peptide comprises
CC   at least one and preferably all D amino acids and/or protecting group(s)
CC   at each terminus. It converts pro-inflammatory high density lipoproteins
CC   (HDL) to anti-inflammatory HDL or makes anti-inflammatory HDL more anti-
CC   inflammatory. The peptide It ranges in length from 3-10 or 6-37
CC   (particularly 18) amino acids and resembles a class A amphipathic helix
CC   of apolipoprotein J (ApoJ). The active agent includes class A amphipathic
CC   helical peptides, class A amphipathic helical peptide mimetics of apoA-I
CC   having aromatic or aliphatic residues in the non-polar face, small
CC   peptides including pentapeptides, tetrapeptides, tripeptides, dipeptides
CC   and pairs of amino acids, Apo-J and peptide mimetics. The active agent is
CC   contained within a polymer which comprises a first layer of a first drug
CC   polymer having a first pharmaceutical characteristic and the polymer
CC   layer comprising a second drug polymer having a second pharmaceutical
CC   characteristic. The stent framework comprises a metallic base or a
CC   polymeric base, especially a material consisting of stainless steel,
CC   nitinol, tantalum, MP35N alloy, platinum, titanium, a suitable
CC   biocompatible alloy and/or biocompatible polymer. The peptide used to
CC   ameliorate symptom(s) of an inflammatory condition e.g. atherosclerosis
CC   or stroke. It is used for; a) mitigating or preventing a coronary
CC   complication associated with an acute phase response to inflammation
CC   where the coronary complication is a symptom of atherosclerosis; b) for
CC   ameliorating a symptom of diabetes or inhibiting restenosis; c) as an
CC   active agent useful in a stent for delivering drugs to a vessel in a
CC   body, especially for treating a vascular condition. The peptide can be
CC   used to treat the symptoms of atherosclerosis (e.g. hypertension, plaque
CC   formation and rupture, reduction in clinical events such as heart attack,
CC   angina or stroke, high levels of plasma cholesterol, high levels of low
CC   density lipoprotein, high levels of very low density lipoprotein or
CC   inflammatory proteins) as well as other inflammatory conditions e.g.
CC   rheumatoid arthritis, lupus erythematous, polyarteritis nodosa,
CC   osteoporosis, alzheimer's disease and viral illnesses such as influenza
CC   A. The peptide is highly stable and readily administered via an oral
CC   route and can be used in the treatment of humans, non-human primates,
CC   canines, equines, felines, porcines, ungulates and largomorphs. This
CC   sequence represents an ApoJ G* amphipathic helical domain peptide used in
CC   the method of the invention.
XX
SQ   Sequence 21 AA;

  Query Match             100.0%;  Score 73;  DB 11;  Length 21;
  Best Local Similarity   100.0%;  Pred. No. 0.00028;
  Matches   15;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 METVAEKALQEYRKK 15
              |||||||||||||||
Db          4 METVAEKALQEYRKK 18
```

Applicant argues that the disclosure of Fogelman does not meet the specific limitations of the claims which are limited to amino acid sequences consisting of SEQ ID NO:1, 2, 3 or 4. This has been considered but not found persuasive. The recitation of "selected from the group

consisting of" limits the group to the recited species, it does not serve to limit the individual amino acid sequences to "consisting of" the sequence identifiers.

Amendment of the claim to recite "Isolated antigenic epitopes of at least one human clusterin isoform selected from the antigenic epitope consisting of SEQ ID NO:1, the antigenic epitope consisting of SEQ ID NO:2, the antigenic epitope consisting of SEQ ID NO:3 or the antigenic epitope consisting of SEQ ID NO:4" would overcome this rejection.

Claim 11 is rejected under 35 U.S.C. 102(b) as being anticipated by Wong et al (European Journal of Biochemistry, 1994, Vol. 221, pp. 917-925). Wong et al disclose the amino acid sequence of human clusterin (page 919, figure 1A) wherein said amino acid sequence comprises the instant SEQ ID NO:2, 3 and 4 at residues 63-78, 93-112 and 431-445, respectively. The amino acid sequence of Wong et al meets the requirement of being antigenic, as said sequence can be bound by an antibody. The sequence also fulfills the specific requirement of "immunogenic" as any amino acid sequence can be immunogenic given the appropriate host and appropriate presentation to said host.

Applicant argues that the disclosure of Wong et al does not meet the specific limitations of the claims which are limited to amino acid sequences consisting of SEQ ID NO:1, 2, 3 or 4. this has been considered but not found persuasive. The recitation of "selected from the group consisting of" limits the group to the recited species, it does not serve to limit the individual amino acid sequences to "consisting of" the sequence identifiers.

Amendment of the claim to recite "Isolated antigenic epitopes of at least one human clusterin isoform selected from the antigenic epitope consisting of SEQ ID NO:1, the antigenic epitope consisting of SEQ ID NO:2, the antigenic epitope consisting of SEQ ID NO:3 or the antigenic epitope consisting of SEQ ID NO:4" would overcome this rejection.

The rejection of claims 1, 5, 6, 11, 15-21 under 35 U.S.C. 102(b) as being anticipated by Yang et al (PNAS, 2000, Vol. 97, pp. 5907-5912) is maintained for reasons of record.

Claim 1 is drawn to oligoclonal antibodies able to recognize and bind the antigenic epitope of at least one glycosylated cytoplasmic or non-glycosylated nuclear isoform of human clusterin, wherein the epitope of the non-glycosylated nuclear isoform is selected from a group

including SEQ ID NO:2 and the non-glycosylated isoform is SEQ ID NO:3 or 4, and wherein the epitope is immunogenic. Claim 5 embodies the antibodies of claim 1 wherein the antibodies are tagged. Claim 6 specifies that the tag is a fluorochrome, a radioactive isotope, an enzyme, biotin or a chemiluminecent substance.

Claim 11 is drawn to an immunogenic antigenic epitopes of at least one human clustering isoform selected from the group consisting of SEQ ID NO:2, 3 or 4.

Claims 20 and 21 are drawn to a kit comprising at least one of the antibodies of claim 1.

Claim 15 is drawn to a method comprising the steps of protein extraction, incubation of the extracted protein with one of the antibodies of claim 1; qualitative and quantitative measurement of the antigen-antibody complexes.

Claim 22 is drawn to use of the antibodies of claim 1 for the qualitative and quantitative determination of the level of at least one isoform of human clusterin in a biological sample. Claim 24 specifies that the determination is carried out by ELISA, RIA, immunohistochemistry and Western blot.

Yang et al disclose a polyclonal antiserum raised by injection of bacterially expressed human clusterin into rabbits , wherein said antiserum is directed against nuclear, nonglycosylated clusterin and is used for immunofluorescence cell staining (page 5907, under "Antibodies") which meets the specific embodiment of claims 5 and 6, requiring a tag and a fluorochrome, respectively. The human clusterin of Yang et al meets the limitations of claim 11 as it reads on epitopes comprising SEQ ID NO:2 ,3 and 4 which are inherently within the clusterin used by Yang et al for immunization of rabbits. Yang et al disclose that an immunological method for detecting the unglycosylated clusterin in nuclear lysates after exposure of the cells to radiation, by measuring binding of the polyclonal antibodies by Western blot, and immunoprecipitation, thus fulfilling the specific limitations of claim 19 and the limitation of claim 17 as requiring a sample which is a "liquor" because a nuclear lysate is a "liquor".

It is noted that the recitation of "for diagnosis of tumors and prediction of their malignancy grade" in claim 20 and the further limitation of specific tumors in claim 21 has not been given patentable weight because the recitation "for diagnosis of tumors and prediction of their malignancy grade" occurs in the preamble of claim 20. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended

use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See In re Hirao, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and Kropa v. Robie, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951). Because the intended use of diagnosing tumors in claim 20 is not given patentable weight, the recitation of the specific tumor types in claim 21 is also lacking patentable weight.

It is further noted neither that the limitation of claim 16 "for the diagnosis of tumors characterized by expression of clusterin and the prediction of their malignancy grade" nor the specific tumors as recited in claim 18 has patentable weight for the exclusion of prior art because the diagnosis of tumors and prediction of malignancy grade are processes of abstract reasoning. not requiring the transformation of matter. As clarified in In re Bilski, 545 F.3d 943, 88 USPQ2d 1385 (Fed. Cir, 2008), a method claim must meet a specialized, limited meaning to qualify as a patent-eligible process claim and the test for such a method claim is whether the claimed method is (1) tied to a particular machine or apparatus, or (2) transforms a particular article to a different state or thing, summarized as the "machine or transformation test". In the instant case, recitation of "diagnosis of tumors characterized by expression of clusterin and the prediction of their malignancy grade" requires neither machine nor transformation beyond those of the active method steps of claim 15 and is therefore not patentable subject matter under 35 U.S.C. 101 and carries no further patentable weigh within the context of the claim..

Given that the method of the prior art comprises the same method steps as claimed in the instant invention, , the claimed method is anticipated because the method will inherently be a method for diagnosis of tumor characterized by expression of clusterin and the prediction of their malignancy grade.. See Ex parte Novitski 26 USPQ 1389 (BPAI 1993).

Applicant argues that the disclosure of Yang et al does not meet the specific limitations of the claims which are limited to amino acid sequences consisting of SEQ ID NO:1, 2, 3 or 4. this has been considered but not found persuasive. The recitation of "selected from the group consisting of" limits the group to the recited species, it does not serve to limit the individual amino acid sequences to "consisting of" the sequence identifiers. In the instant case of claim 1, applicant has used "selected from the group of amino acid sequences consisting of" and then

recites species A, B, C and D. In order for the claim to be a proper Markush group, the term "consisting of" must be applied to the group, not to the individual SEQ ID NO.

Amendment of claim 11 to recite "Isolated antigenic epitopes of at least one human clusterin isoform selected from the antigenic epitope consisting of SEQ ID NO:1, the antigenic epitope consisting of SEQ ID NO:2, the antigenic epitope consisting of SEQ ID NO:3 or the antigenic epitope consisting of SEQ ID NO:4" would overcome the rejection of claim 11.

Amendment of claim 12 to recite "A method for the preparation of oligoclonal antibodies which comprises the following steps: solid phase synthesis of at least one human clusterin isoform selected from the antigenic epitope consisting of SEQ ID NO:1, the antigenic epitope consisting of SEQ ID NO:2, the antigenic epitope consisting of SEQ ID NO:3 or the antigenic epitope consisting of SEQ ID NO:4;

conjugation of the at least one antigenic epitopes with a proteic carrier in order to make the epitope immunogenic;

animal immunization with said immunogenic epitope in complete Freund's adjuvant; and,

serum withdrawal from the immunized animal and purification of the oligoclonal antibodies" would overcome the rejection of claims 12-14.

Even if amended to clearly recite "Isolated oligoclonal antibodies able to recognize and bind the antigenic epitope of at least one glycosylated cytoplasmic or non glycosylated nuclear isoform of human clusterin in a selective and specific way, wherein the antigenic epitope of the non-glycosylated nuclear isoform is the antigenic epitope consisting of SEQ ID NO:1, or the antigenic epitope consisting of SEQ ID NO:2, and the antigenic epitope of the glycosylated cytoplasmic isoform is the antigenic epitope consisting of SEQ ID NO:3 or the antigenic epitope consisting of SEQ ID NO:4", claims 1, 5, 6, 15-21 would remain rejected by Yang et al, because immunization with the bacterially expressed human clusterin of Yang et al inherently produces a polyclonal antiserum comprising the oligoclonal antibodies that bind to the non-glycosylated nuclear isoform consisting of SEQ ID NO:2 as evidenced by the binding of the polyclonal antiserum to the 55-kDa inducible protein.

It is noted that the instant SEQ ID NO:1 is novel over the prior art, and the disclosure of Yang et al does not anticipate the oligoclonal antibodies which binds to the amino acid sequence consisting of SEQ ID NO:1, 3 or 4.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 5, 11-18, 20 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over O'Sullivan et al (Cell Death and Differentiation, 2003, vol. 10, pp. 914-927) in view of Wong et al (European Journal of Biochemistry, 1994, Vol. 221, pp. 917-925) and Maloy and Coligan ('Selection of Immunogenic Peptides for antisera Production', In: Current Protocols in Immunology, 1991, pp. 9.3.1-9.3.5, cited in a previous action).

O'Sullivan et al teach that in cells undergoing apoptosis after treatment with TNF-alpha or ICI, clusterin can be detected in the nuclear fraction as a non-glycosylated, uncleaved isoform (page 922, bridging paragraph, column 1 to column 2). O'Sullivan et al teach that during normal synthesis and secretion, clusterin is translocated to the lumen of the ER where it is folded and glycosylated (page 921, first column, lines 1-5). O'Sullivan et al teach that human clusterin has six N-linked glycosylation sites including alpha-81N (page 914, lines 28-31). O'Sullivan et al teach that it was not possible to distinguish if the nascent clusterin was not glycosylated as a

result of the TNF-alpha or ICI treatment, or if glycosylated clusterin was deglycosylated prior to retrograde transport to the ER and then the nucleus (page 922, second column, lines 2-9).

Wong et al teach the sequence surrounding the six glycosylation sites in human clusterin including alpha-81N, which is the second glycosylation site indicated in Figure 1A and includes the instant SEQ ID NO:2.

Maloy and Coligan teach that the length of the peptide of about 15 residues can be used to make an antisera that will react with the native protein (page 9.3.3, under the heading "Selection of the Length of the Peptide").

It would have been prima facie obvious at the time that the claimed invention was made to raise antibodies using pairs of peptides representing the glycosylation sites of clusterin indicated in Wong et al, wherein said peptide pair comprised a glycosylated peptide and a non-glycosylated peptide, thus providing a polyclonal antiserum which binds to the epitope f the instant SEQ ID NO:2 when both glycosylated and non-glycosylated. One of skill in the art would have been motivated to do so in order to have antibodies that bind to clusterin at specific epitopes that were either glycosylated or non-glycosylated. One of skill in the art would understand that having antibodies which can map the glycosylation or non-glycosylation of the clusterin protein can further the understanding of the processing and function of the clusterin. It would have been further obvious to use the art-recognized procedure of Maloy and Coligan to raise the antibodies in order to obtain an antiserum that will bind to the native protein.

Applicant argues that none of the cited references provide for the specific limitations of the claims which are limited to amino acid sequences consisting of SEQ ID NO:1, 2, 3 or 4. this has been considered but not found persuasive. The recitation of "selected from the group consisting of" limits the group to the recited species, it does not serve to limit the individual amino acid sequences to "consisting of" the sequence identifiers. In the instant case of claim 1, applicant has used "selected from the group of amino acid sequences consisting of" and then recites species A, B, C and D. In order for the claim to be a proper Markush group, the term "consisting of" must be applied to the group, not to the individual SEQ ID NO.

Amendment of claim 1 to recite "Isolated oligoclonal antibodies able to recognize and bind the antigenic epitope of at least one glycosylated cytoplasmic or non glycosylated nuclear isoform of human clusterin in a selective and specific way, wherein the antigenic epitope of the

non-glycosylated nuclear isoform is selected from the antigenic epitope consisting of SEQ ID NO:1, the antigenic epitope consisting of SEQ ID NO:2, the antigenic epitope consisting of SEQ ID NO:3 or the antigenic epitope consisting of SEQ ID NO:4" would over come this rejection of claims 1, 5, 15-18, 20 and 21.

Amendment of claim 11 to recite "Isolated antigenic epitopes of at least one human clusterin isoform selected from the antigenic epitope consisting of SEQ ID NO:1, the antigenic epitope consisting of SEQ ID NO:2, the antigenic epitope consisting of SEQ ID NO:3 or the antigenic epitope consisting of SEQ ID NO:4" would overcome the rejection of claim 11.

Amendment of claim 12 to recite "A method for the preparation of oligoclonal antibodies which comprises the following steps: solid phase synthesis of at least one human clusterin isoform selected from the antigenic epitope consisting of SEQ ID NO:1, the antigenic epitope consisting of SEQ ID NO:2, the antigenic epitope consisting of SEQ ID NO:3 or the antigenic epitope consisting of SEQ ID NO:4;

conjugation of the at least one antigenic epitopes with a proteic carrier in order to make the epitope immunogenic;

animal immunization with said immunogenic epitope in complete Freund's adjuvant; and,

serum withdrawal from the immunized animal and purification of the oligoclonal antibodies" would overcome the rejection of claims 12-14.

Claims 1, 5-8, 10-18, 20 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over O'Sullivan et al (Cell Death and differentiation, 2003, vol. 10, pp. 914-927) in view of Wong et al (European Journal of Biochemistry, 1994, Vol. 221, pp. 917-925) and Maloy and Coligan ('Selection of Immunogenic Peptides for antisera Production', In: Current Protocols in Immunology, 1991, pp. 9.3.1-9.3.5). as applied to claims 1, 5, 11-18, 20 and 21 above, and further in view of Kerr and Thorpe (Immunochemistry LabFax, 1994, pages ix-x, 118, 134-135, 142-143, 158-161).

Claim 6 embodies the antibodies of claim 65, wherein the antibodies are tagged with a fluorochrome, radioactive isotope, enzyme, biotin or a chemiluminescent substrate. Claim 7

specifies that said fluorochrome is selected from the group consisting of fluorescein, ficoerttrine, rhodamine, texas red and cumarine. Claim 8 specifies that said isotope is 14-C or 3-H. Claim 10 specifies that the enzyme is horseradish peroxidase or alkaline phosphatase.

Kerr and Thorpe et al teach common methods in immunoassays, and commonly used antibody labeling tags including fluorochromes (pp. 158-161), isotopes (page 118) and the enzymes horseradish peroxidase (pp. 134-135) and alkaline phosphatase (pp. 142-143).

It would have been prima facie obvious at the time that the claimed invention was made to label the antibodies rendered obvious by the combined teachings of O'Sullivan et al, Wong et al and Maloy and Coligan with fluorochromes, isotopes, horseradish peroxidase or alkaline phosphatase. One of skill in the art would have been motivated to do so because these were tags commonly recognized in the art to be useful in labeling antibodies.

Applicant argues that none of the cited references provide for the specific limitations of the claims which are limited to amino acid sequences consisting of SEQ ID NO:1, 2, 3 or 4. this has been considered but not found persuasive. The recitation of "selected from the group consisting of" limits the group to the recited species, it does not serve to limit the individual amino acid sequences to "consisting of" the sequence identifiers. In the instant case of claim 1, applicant has used "selected from the group of amino acid sequences consisting of" and then recites species A, B, C and D. In order for the claim to be a proper Markush group, the term "consisting of" must be applied to the group, not to the individual SEQ ID NO.

Amendment of claim 1 to recite "Isolated oligoclonal antibodies able to recognize and bind the antigenic epitope of at least one glycosylated cytoplasmic or non glycosylated nuclear isoform of human clusterin in a selective and specific way, wherein the antigenic epitope of the non-glycosylated nuclear isoform is the antigenic epitope consisting of SEQ ID NO:1, or the antigenic epitope consisting of SEQ ID NO:2, and the antigenic epitope of the glycosylated cytoplasmic isoform is the antigenic epitope consisting of SEQ ID NO:3 or the antigenic epitope consisting of SEQ ID NO:4" would over come this rejection of claims 1, 5-8, 15-18, 20 and 21.

Amendment of claim 11 to recite "Isolated antigenic epitopes of at least one human clusterin isoform selected from the antigenic epitope consisting of SEQ ID NO:1, the antigenic epitope consisting of SEQ ID NO:2, the antigenic epitope consisting of SEQ ID NO:3 or the antigenic epitope consisting of SEQ ID NO:4" would overcome the rejection of claim 11.

Amendment of claim 12 to recite "A method for the preparation of oligoclonal antibodies which comprises the following steps: solid phase synthesis of at least one human clusterin isoform selected from the antigenic epitope consisting of SEQ ID NO:1, the antigenic epitope consisting of SEQ ID NO:2, the antigenic epitope consisting of SEQ ID NO:3 or the antigenic epitope consisting of SEQ ID NO:4;

conjugation of the at least one antigenic epitopes with a proteic carrier in order to make the epitope immunogenic;

animal immunization with said immunogenic epitope in complete Freund's adjuvant; and,

serum withdrawal from the immunized animal and purification of the oligoclonal antibodies" would overcome the rejection of claims 12-14.

Claims 1, 5, 6, 9, 10-18, 20 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over O'Sullivan et al (Cell Death and differentiation, 2003, vol. 10, pp. 914-927) in view of Wong et al (European Journal of Biochemistry, 1994, Vol. 221, pp. 917-925) and Maloy and Coligan ('Selection of Immunogenic Peptides for antisera Production', In: Current Protocols in Immunology, 1991, pp. 9.3.1-9.3.5). as applied to claims 1, 5, 11-18, 20 and 21 above, and further in view of Scheele et al (U.S. 5,663,315).

Scheele et al teach common methods for labeling and detecting antibodies include the use of radioisotopes, fluorophores, horseradish peroxidase and luciferin (column 5,lines 12-34).

It would have been prima facie obvious at the time that the claimed invention was made to use radioisotopes, fluorophores, horseradish peroxidase or luciferin for tagging the antibodies rendered obvious by the combined teachings of O'Sullivan et al, Wong et al and Maloy and Coligan. One of skill in the art would have been motivated to do so because these were tags commonly recognized in the art to be useful in labeling antibodies.

Applicant argues that none of the cited references provide for the specific limitations of the claims which are limited to amino acid sequences consisting of SEQ ID NO:1, 2, 3 or 4. this has been considered but not found persuasive. The recitation of "selected from the group consisting of" limits the group to the recited species, it does not serve to limit the individual amino acid sequences to "consisting of" the sequence identifiers. In the instant case of claim 1,

applicant has used "selected from the group of amino acid sequences consisting of" and then recites species A, B, C and D. In order for the claim to be a proper Markush group, the term "consisting of" must be applied to the group, not to the individual SEQ ID NO.

Amendment of claim 1 to recite "Isolated oligoclonal antibodies able to recognize and bind the antigenic epitope of at least one glycosylated cytoplasmic or non glycosylated nuclear isoform of human clusterin in a selective and specific way, wherein the antigenic epitope of the non-glycosylated nuclear isoform is the antigenic epitope consisting of SEQ ID NO:1, or the antigenic epitope consisting of SEQ ID NO:2, and the antigenic epitope of the glycosylated cytoplasmic isoform is the antigenic epitope consisting of SEQ ID NO:3 or the antigenic epitope consisting of SEQ ID NO:4" would over come this rejection of claims 1, 5-8, 15-18, 20 and 21.

Amendment of claim 11 to recite "Isolated antigenic epitopes of at least one human clusterin isoform selected from the antigenic epitope consisting of SEQ ID NO:1, the antigenic epitope consisting of SEQ ID NO:2, the antigenic epitope consisting of SEQ ID NO:3 or the antigenic epitope consisting of SEQ ID NO:4" would overcome the rejection of claim 11.

Amendment of claim 12 to recite "A method for the preparation of oligoclonal antibodies which comprises the following steps: solid phase synthesis of at least one human clusterin isoform selected from the antigenic epitope consisting of SEQ ID NO:1, the antigenic epitope consisting of SEQ ID NO:2, the antigenic epitope consisting of SEQ ID NO:3 or the antigenic epitope consisting of SEQ ID NO:4;

conjugation of the at least one antigenic epitopes with a proteic carrier in order to make the epitope immunogenic;

animal immunization with said immunogenic epitope in complete Freund's adjuvant; and,

serum withdrawal from the immunized animal and purification of the oligoclonal antibodies" would overcome the rejection of claims 12-14.

All claims are rejected.

All objections and rejections as set forth of maintained in the prior Office action are withdrawn.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10-6:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571)272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Karen A Canella/
Primary Examiner, Art Unit 1643